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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,331	09/16/2003	Laurent Humeau	397272000401	4194

25225 7590 12/07/2009

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EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
12/07/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/664,331	HUMEAU ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *15,17,19-21,23,48,50,53,57,85-87,93,97,100 and 101* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/30/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-3,5,6,8-15,17-23,29,30,33-35,38,40-43,45,47,48,50,52,53,56-59,61-64,66-71,83,85-88,90,93 and 97-101.

Continuation of Disposition of Claims: Claims rejected are 1-3,5,6,8-14,18,22,29,30,33-35,38,40-43,45,47,52,56,58,59,61-64,66-71,83,88,90,98 and 99.

Detailed Office Action

Status of the Claims

Acknowledgement is hereby made of receipt and entry of the communication filed 03 September, 2009. Claims 1-3, 5, 6, 8-15, 17-23, 29, 30, 33-35, 38, 40-43, 45, 47, 48, 50, 52, 53, 56-59, 61-64, 66-71, 83, 85-88, 90, 93, and 97-101 are currently under examination. Claims 1-3, 5, 6, 8-14, 18, 22, 29, 30, 33-35, 38, 40-43, 45, 47, 52, 56, 58, 59, 61-64, 66-71, 83, 88, 90, 98, and 99 read on the elected invention. Claims 15, 17, 19-21, 23, 48, 50, 53, 57, 85-87, 93, 97, 100, and 101 stand withdrawn from further consideration as being directed toward a nonelected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 C.F.R. § 1.144). See M.P.E.P. § 821.01.

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The previous rejection of claims 1-3, 5-14, 18, 22, 29, 30, 33-35, 38, 40-43, 45, 47, 52, 56, 58, 59, 61-64, 66-71, 83, 84, 88, 90, 94, 98, and 99 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is hereby withdrawn in response to Applicants' amendment.

35 U.S.C. § 103(a)

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The previous rejection of claims 1-3, 5-14, 18, 22, 29, 30, 33, 69, 78, 83, and 98 under 35 U.S.C. § 103(a) as being unpatentable over Costello *et al.* (2000) in view of Quinn *et al.* (1998), is hereby withdrawn in response to Applicants' amendment.

The previous rejection of claims 34, 35, 38, 40-43, 45, 47, 52, 56, 58, 59, 61-64, 66-69, 83, 69, 78, 83, and 98 under 35 U.S.C. § 103(a) as being unpatentable over Costello *et al.* (2000) in view of Quinn *et al.* (1998), is hereby withdrawn in response to Applicants' amendment.

The previous rejection of claims 88, 90, and 99 under 35 U.S.C. § 103(a) as being unpatentable over Costello *et al.* (2000) in view of Quinn *et al.* (1998), is hereby withdrawn in response to Applicants' amendment.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 1-3, 5, 6, 8-14, 18, 22, 29, 30, 33, 34, 35, 38, 40-43, 45, 47, 52, 56, 58, 59, 61-64, 66-71, 83, 88, 90, 98, and 99 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398, (Fed. Cir. 1997). *Fiers v. Revel Co.*, 984 F.2d 1164, 25 U.S.P.Q.2d 1601, (Fed. Cir. 1993). *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 U.S.P.Q.2d 1016, (Fed. Cir. 1991). *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2d 1609, (Fed. Cir. 2002). *Univ. of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 920, 69 U.S.P.Q.2d 1886, (Fed. Cir. 2004).*In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976). *University of Rochester* v. *G. D. Searle & Co., Inc.*, 358 F.3d 916, 69 U.S.P.Q.2d 1886 (C.A.F.C. 2004).

The claims have been amended to require a transduction efficiency of at least 90%. As previously set forth, in order to

satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Vas-Cath, Inc., v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116. The issue raised in this application is whether the original application provides adequate support for the broadly claimed genus of cell surface binding molecules and cell types transduced with said molecules and a lentiviral vector. Specifically, claim 1 simply references a "polypeptide which binds said cell surface by binding to a T cell surface receptor". Claim 34 specifies that "at least one polypeptide that physically interacts with a receptor on the surface of the primary T cell or T stem cell". Finally, claim 71 simply states that a "cell surface binding polypeptide" is employed. Thus, all of the claims encompass a large sundry class of both ligands (e.g., any polypeptide that binds to the target) and receptors (e.g., any T-cell surface receptor). The purpose of the method is to provide a stable transduction by making the T-cell more receptive to the lentiviral vector of interest.

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of

the invention and its function. A biomolecule sequence described only by functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the biomolecule of interest. *In re Bell*, 991 F.2d 781, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993). *In re Deuel*, 51 F.3d 1552, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995). A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 U.S.P.Q.2d 1895, 1905 (Fed. Cir. 1995). The court noted in this decision that a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not reasonably lead those skilled in the art to any particular species.

An applicant may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. For some biomolecules, examples of identifying characteristics

include a nucleotide or amino acid sequence, chemical structure, binding affinity, binding specificity, and molecular weight. The written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. Without such a correlation, the capability to recognize or understand the structure form the mere recitation of function and minimal structure is highly unlikely. In the latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement. *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566, 43 U.S.P.Q.2d 1398, 1404, 1406 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998). *In re Wilder*, 736 F.2d 1516, 1521, 222 U.S.P.Q. 369, 372-3 (Fed. Cir. 1984). Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

The claims of the instant application are broadly directed toward a large genus of poorly defined cell surface binding polypeptides and potential T-cell surface targets. Concerning the cell surface binding polypeptides, this term encompasses an inordinate number of species with disparate structures and functions. The term could encompass antibodies that bind to any given cell surface receptor, natural ligands, peptidomimetics, polypeptide fragments, or mutants. These polypeptides could bind to a specific binding site (like a ligand-receptor binding interaction), they could bind outside this region, or they could

bind in a non-specific manner. The disclosure fails to sufficient guidance pertaining to the structural, functional, and physicochemical characteristics of any given polypeptide. It is noted that a laundry list of various polypeptides is provided. However, as noted *supra*, the courts have clearly stated that simply providing a "laundry" list of all possible permutations does not put the applicant in possession of the full genus of compounds. There must be a teaching in the specification that leads the skilled artisan to a particular class of compounds.

The specification also fails to provide adequate guidance pertaining to the T-cell surface receptor of interest. Human T-cells encode a large number of cell surface molecules with disparate structures and functions. However, the disclosure fails to reasonably identify those cell surface receptors that should be targets of the invention. Which T-cell surface receptors can be modulated in such a manner that they will make the cell more receptive to lentiviral transduction? Which portions of these cell surface molecules should be targeted by the polypeptides of interest? What are the molecular determinants modulating these interactions? The disclosure fails to provide sufficient structural and functional information concerning these items. Considering the unpredictability of the art, the failure of the disclosure to provide a strong structural/functional nexus between any of the cell surface binding polypeptides and their targets, the large breadth of the claimed invention, and the limited number of examples set forth in the specification, the skilled artisan would reasonably conclude the applicants were not in full possession of the genus of cell surface binding polypeptides and cell targets at the

time of filing.

Response to Arguments

Applicants traverse and submit that the claim amendments and specification provide adequate support for the claimed genus of polypeptides and cell surface molecules. Specifically the term "cell stimulatory polypeptide" has been further defined to encompass an antibody, antigen binding fragment, or ligand. These arguments are not found to be persuasive for the reasons set forth *supra*. The disclosure fails to provide adequate structural and functional guidance pertaining to those molecules that will function in the desired manner, particularly those combinations of cell stimulatory polypeptides that will lead to a 90% transduction efficiency. The disclosure only provides two limited embodiments wherein 90% transduction frequencies were obtained. One example involved α-CD3 and α-CD28 Mabs administered post-transduction in conjunction with a retroviral vector and $CD4^+$ lymphocytes. The second example involved the FLT-3 ligand, TPO, and the Kit-ligand in conjunction with $CD34^+$ cells and a lentiviral vector. Thus, selection of the cell stimulatory molecule, cell target, expression vector, and administration regimen are all critical to the success of the claimed invention. Applicants simply provide a sundry list of over a hundred potential cell surface binding partners (e.g., see p. 6) without providing any detailed guidance pertaining to which antibodies, antigen binding fragments, or ligands can reasonably be expected to function in the desired manner. Clearly, the skilled artisan would reasonably conclude that Applicants were not in possession of the claimed invention at the time of filing.

Scope of Enablement

Claims 1-3, 5, 6, 8-14, 18, 22, 29, 30, 33, 34, 35, 38, 40-43, 45, 47, 52, 56, 58, 59, 61-64, 66-71, 83, 88, 90, 98, and 99 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The claims have been amended to require a transduction efficiency of at least 90%. The disclosure only provides two limited embodiments wherein 90% transduction frequencies were obtained. One example involved α-CD3 and α-CD28 Mabs administered post-transduction in conjunction with a retroviral vector and $CD4^+$ lymphocytes. The second example involved the FLT-3 ligand, TPO, and the Kit-ligand administered post-transduction in conjunction with $CD34^+$ cells and a lentiviral vector. Appropriately drafted claim language directed toward these embodiments would be acceptable. However, the specification fails to support the full breadth of the claim language directed toward the various cell targets, cell stimulatory polypeptides, expression vectors, and transduction regimens.

The legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or

guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide adequate guidance pertaining to the identification of suitable cell stimulatory polypeptides. The claims simply specify that an antibody, antigen binding fragment, or ligand can be employed. A list of over a hundred sundry potential cell surface binding partners (e.g., see p. 6) is disclosed in the specification. However, with the exception of those examples noted above, the disclosure fails to identify those cell stimulatory molecules that can reasonably be expected to produce 90% transduction efficiencies.

2) The disclosure fails to adequately identify a suitable number of cell targets and target molecules that can be exploited to obtain a 90% transduction efficiency. The claims are broadly directed toward lymphoid, myeloid, or hematopoietic stem cells. Each of these groups of cells will display different cell surface ligands depending upon the differentiation state. Moreover, many of these populations may actually encompass a heterogenous cell population with genotypically and phenotypically distinct sub-populations. Thus, it is not readily manifest that 90% transduction efficiencies can be obtained without first carefully identifying suitable cell stimulatory partners, the appropriate viral vector, and transduction regimen.

3) The disclosure fails to provide adequate guidance pertaining to the identification of suitable viral vectors that will function in the desired manner.

4) The claim breadth is excessive and inadequately supported by the disclosure. The broadest claims are not limited to any particular combination of cell stimulatory polypeptides, specific cell targets, viral vectors, or transduction regimen. Yet the prior art suggests this combination of factors is critical to achieve the claimed levels of transduction efficiency.

5) The prior art teaches that it is extremely difficult to obtain transduction efficiencies of 90% (Quinn *et al.*, 1998; Costello *et al.*, 2000; Schroers *et al.*, 2000). As already noted several factors influence the transduction efficiency including the cell target/population, cell stimulatory molecules employed, viral vectors utilized, and transduction regimen.

6) Considering the claim breadth, unpredictability of the art, and limited guidance provided by the disclosure, clearly there are an insufficient number of working embodiments to enable the full breadth of the claim language.

When all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Action Is Final, Necessitated by Amendment

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). A shortened statutory period for reply to

this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Larry R. Helms, can be reached at (571) 272-0832. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: a) faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), b) hand carried or delivered to the Customer Service Window (now located at the Randolph Building, 401 Dulany Street, Alexandria, VA 22314), c) mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or d) transmitted to the Office using the Office's Electronic Filing System. This notice replaces all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized Delivery and Facsimile Transmission Policy for Patent Related Correspondence, and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

/Jeffrey S. Parkin/

Jeffrey S. Parkin, Ph.D.
Primary Examiner, Art Unit 1648

23 November, 2009